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EXAMINER	
JANSSEN, SHANNON L	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
03/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/537,588	PASCHKE, MATTHIAS	
	Examiner	Art Unit	
	SHANNON JANSSEN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 24-30* is/are pending in the application.

4a) Of the above claim(s) *2, 10-21 and 24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2005 and 02 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *September 2, 2005 and December 16, 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21 and 24-30 are currently pending. The amendment received December 16, 2009 amended claims 4 and 9. Claims 2, 10-21 and 24-30 have been withdrawn and claims 1 and 3-9 are currently under consideration.

Election/Restrictions

Applicant's elected Group I, claims 1-9, with traverse in the reply filed on June 22, 2009 and further clarified on July 7, 2009.

Claims 10-21 and 24-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Inventions, there being no allowable generic or linking claim.

Applicant's elected species of (a) a first fusion protein fragment: phage coat protein (claim 4) and a second fusion protein fragment: a protein encoded by a cDNA (claim 3), (b) interaction domain for a first protein: a leucine zipper domain (claim 6) and interaction domain for a second protein: a leucine zipper domain (claim 6), and (c) a translocation sequence for a first fusion protein: a Sec-dependent sequence (claim 7) and a translocation sequence for a first fusion protein: a Tat-dependent sequence (claim 8) **without** traverse in the reply filed on June 22, 2009 and further clarified in the response filed on July 7, 2009.

Claim 2 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to German application 10256669.0, filed December 4, 2002. Receipt is

acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. It is noted that applicant cannot rely upon the foreign priority papers to overcome a rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. The present application also claims status as a National Stage entry of PCT/EP2003/013709, filed December 4, 2003.

Information Disclosure Statement

The information disclosure statements filed September 2, 2005 and December 16, 2009 have been considered by the examiner.

Applicant is requested to provide references cited in the information disclosure statement filed June 6, 2005. The references were not forwarded by the International Bureau.

Withdrawn Rejections

The rejection of claims 4-5 and 9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the claim amendments.

Invention as claimed

The present invention is drawn to a protein mixture comprising: a) at least a first fusion protein comprising: i) a protein or protein fragment, ii) an interaction domain and iii) a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially unfolded state, and b) at least a second fusion protein comprising: i) a protein or protein fragment, ii) an interaction domain and iii) a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially folded state,

wherein the interaction domain of the first fusion protein can bind to those of the second fusion protein, and various embodiments.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-7, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Crameri et al. (Display of biologically active proteins on the surface of filamentous phages: a cDNA cloning system for selection of functional gene products linked to the genetic information responsible for their production, 1993, Gene, vol 137, pp 69-75).

Regarding present **claim 1**, Crameri et al. teach a) a first fusion protein comprising: i) PIII (i.e.: a protein or protein fragment; see p 70, col 2, para 2), ii) a Jun Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2), and iii) wherein PIII is the phage coat protein comprising the pelB signal sequence (i.e.: a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane in an essentially unfolded state; see p 70, col 1, para 4, col 2, para 2, Fig. 1), and b) a second fusion protein comprising: i) a cDNA from a cDNA library (i.e.: protein or protein fragment), ii) a Fos Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2,and iii) a pelB signal sequence (i.e.: a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane),

wherein the interaction domain of the first fusion protein can bind to those of the second fusion protein (throughout document, see particularly p 70, col 1, para 4, Fig. 1). **Note:** the limitations regarding folding state (e.g.: that the fusion protein is translocated in an essentially folded or unfolded state) are not given patentable weight because they are interpreted as a process of making and not the end product currently claimed (e.g.: a specific structure that would provide different folding requirements is not presently in the claims).

Regarding present **claim 3**, Crameri et al. teach a second fusion protein comprising a cDNA from a cDNA library (see p 70, col 1, para 4, Fig. 1).

Regarding **claims 4-5**, Crameri et al. teach the M13 pIII phage coat protein (see p 70, col 2, para 2).

Regarding **claim 6**, Crameri et al. teach the first fusion protein with a Jun leucine zipper interaction domain and the second fusion protein with a Fos leucine zipper interaction domain (see p 70, col 2, para 2).

Regarding **claim 7**, Crameri et al. teach wherein the first fusion protein comprises the pelB signal sequence (i.e.: Sec-dependent signal sequence; see p 70, col 1, para 4, col 2, para 2, Fig. 1).

Regarding **claim 9**, Crameri et al. teach covalent linking of the Jun and Fos leucine zippers (i.e.: the first fusion protein is covalently bound to the second fusion protein through the leucine zippers; see p 70, col 1, para 4, Fig. 1).

Therefore, the teachings of Crameri et al. anticipate present claims 1, 3-7, and 9.

Response to Arguments

Applicant's arguments filed December 16, 2009 have been fully considered but they are not persuasive for the following reasons.

In response to applicants arguments that Crameri et al. do not teach the limitation of the second fusion protein comprising a translocation sequence that leads to translocation in a folded state, it is noted that the limitations regarding folding state (e.g.: that the fusion protein is translocated in an essentially folded or unfolded state) are not given patentable weight because they are interpreted as a process of making and not the end product currently claimed (e.g.: a specific structure that would provide different folding requirements is not presently in the claims). Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product by process claim is the same as or obvious from a product of the prior art, the claim is unpatentably distinct even though the prior product was made by a different process, *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966(Fed. Cir. 1985).

The structure implied by the process steps should be considered when assessing the patentability of product -by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would by expected to impart distinctive structural characteristics to the final product, See e.g., *In re Garnero*, 412 F. 2d 276, 279, 162 USPQ 221, 223 (CCPA 1979). Applicants do not currently have a specific structure (e.g.: a specific sequence) in the claims that would provide specific folding requirements.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 3-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crameri et al. (Display of biologically active proteins on the surface of filamentous phages: a cDNA cloning system for selection of functional gene products linked to the genetic information responsible for their production, 1993, Gene, vol 137, pp 69-75) and Weiner et al. (US Patent 6,335,178, granted January 1, 2002), as evidenced by Wu et al. (Membrane targeting and translocation of bacterial hydrogenases, 2000, Arch Microbiol, Vol 173, pp 319-324).

Regarding present **claim 1**, Crameri et al. teach a) a first fusion protein comprising: i) PIII (i.e.: a protein or protein fragment; see p 70, col 2, para 2), ii) a Jun Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2), and iii) wherein PIII is the phage coat protein comprising the pelB signal sequence (i.e.: a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic

membrane in an essentially unfolded state; see p 70, col 1, para 4, col 2, para 2, Fig. 1), and b) a second fusion protein comprising: i) a cDNA from a cDNA library (i.e.: protein or protein fragment), ii) a Fos Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2,and iii) a pelB signal sequence (i.e.: a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane), wherein the interaction domain of the first fusion protein can bind to those of the second fusion protein (throughout document, see particularly p 70, col 1, para 4, Fig. 1).

Regarding present **claim 3**, Crameri et al. teach a second fusion protein comprising a cDNA from a cDNA library (see p 70, col 1, para 4, Fig. 1).

Regarding **claims 4-5**, Crameri et al. teach the M13 pIII phage coat protein (see p 70, col 2, para 2).

Regarding **claim 6**, Crameri et al. teach the first fusion protein with a Jun leucine zipper interaction domain and the second fusion protein with a Fos leucine zipper interaction domain (see p 70, col 2, para 2).

Regarding **claim 7**, Crameri et al. teach wherein the first fusion protein comprises the pelB signal sequence (i.e.: Sec-dependent signal sequence; see p 70, col 1, para 4, col 2, para 2, Fig. 1).

Regarding **claim 9**, Crameri et al. teach covalent linking of the Jun and Fos leucine zippers (i.e.: the first fusion protein is covalently bound to the second fusion protein through the leucine zippers; see p 70, col 1, para 4, Fig. 1).

Although Crameri et al. teach first and second fusion proteins covalently bound, Crameri et al. do not teach a second fusion protein comprising a Tat-dependent translocation sequence.

Regarding present **claims 1 and 8**, Weiner et al. (as evidenced by Wu et al., where the Mtt pathway and the Tat pathway are the same pathway; see abstract, p 319, col 2) teach a Tat-dependent translocation sequence that transports folded proteins through the cytoplasmic membrane (see Weiner et al., col 1, 2, 10, and examples 1-5).

It would have been obvious to one of skill in the art to use the Tat-dependent translocation sequence taught by Weiner et al. in the fusion protein mixture taught by Crameri et al. One would have been motivated to do so to take advantage of the ability of the Tat pathway to transport folded proteins. One would have had a reasonable expectation for success because Weiner et al. teach that the translocation sequences translocate functional folded proteins through the cell membrane (see col 1, 2, 10, and col 35, para 2 - col 36, para 1). Therefore, the teachings of Crameri et al. and Weiner et al. render the present invention to be *prima facie* obvious.

Response to Arguments

Applicant's arguments filed December 16, 2009 have been fully considered but they are not persuasive for the following reasons.

In response to applicants arguments that Crameri et al. do not teach the limitation of the second fusion protein comprising a translocation sequence that leads to translocation in a folded state, it is noted that the limitations regarding folding state (e.g.: that the fusion protein is translocated in an essentially folded or unfolded state) are not given patentable weight because they are interpreted as a process of making and not the end product currently claimed (e.g.: a specific structure that would provide different folding requirements is not presently in the claims). Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does

not depend on its method of production. If the product in the product by process claim is the same as or obvious from a product of the prior art, the claim is unpatentably distinct even though the prior product was made by a different process, *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966(Fed. Cir. 1985).

The structure implied by the process steps should be considered when assessing the patentability of product –by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would by expected to impart distinctive structural characteristics to the final product, See e.g., *In re Garnero*, 412 F. 2d 276, 279, 162 USPQ 221, 223 (CCPA 1979). Applicants do not currently have a specific structure (e.g.: a specific sequence) in the claims that would provide specific folding requirements.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, all the references teach proteins with translocation sequences relating to folding and transportation into the periplasmic space or extracellular matrix. In addition, Weiner et al. state:

"Such translocation offers a unique advantage over current methodologies for protein purification. Because the composition of culture medium can be manipulated, and because the periplasm contains only about 3% of the proteins of gram negative bacteria, expressed proteins which are translocated into the extracellular medium or into the periplasm are more likely to be expressed as functional soluble proteins than if they were translocated to cellular membranes or to the cytoplasm. Furthermore, translocation to the periplasm or to the extracellular medium

following protein expression in the cytoplasm allows the expressed protein to be correctly folded by cytoplasmic enzymes prior to its translocation, thus allowing retention of the expressed protein's biological activity." (See col 10).

Therefore, one of skill in the art would have been motivated to utilize the Tat sequence taught by Weiner et al. in order to take advantage of the benefits taught by Weiner et al.

Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute one known element (i.e.: the Tat translocation sequence taught by Weiner et al.) for another known element (i.e.: the PelB translocation sequence taught by Crameri et al.) because it would have yielded the predictable result of a folded protein. See *KSR International Co. v. Teleflex Inc.*, USPQ2d 1385 (U.S. 2007).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that one of the fusion proteins is folded in the cytoplasm and is subsequently transported into the periplasm, where it can bind to another fusion protein which has been folded in the periplasm) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, the limitation that the first fusion protein and second fusion protein are covalently or non-covalently bound is not required to take place in any particular location (e.g.: it is not required to take place in a cell) and therefore applicants arguments regarding whether a protein folded in the cytoplasm would interact with a protein folded in the periplasm do not apply.

In response to applicants arguments that Crameri et al. teach away from the claimed invention, disclosed examples and preferred embodiments do not constitute a teaching away

from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). See MPEP § 2123. In addition, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). See MPEP § 2141.06 IV. The fact that Crameri et al. do not contemplate the use of a Tat translocation sequence does not constitute "teaching away". In addition, the fact that Crameri et al. state "the potential for the expression of dimmers is mainly limited by the imagination of the investigator" would indicate that Crameri et al. are encouraging investigators to be creative and contemplate other possibilities.

Claims 1 and 3-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crameri et al. (Display of biologically active proteins on the surface of filamentous phages: a cDNA cloning system for selection of functional gene products linked to the genetic information responsible for their production, 1993, Gene, vol 137, pp 69-75) and Georgiou et al. (US Patent 7,419,783, filed November 5, 2002, with benefit to provisional applications 60/404944, filed August 21, 2002, and 60/337452, filed November 5, 2001).

Regarding present **claim 1**, Crameri et al. teach a) a first fusion protein comprising: i) PIII (i.e.: a protein or protein fragment; see p 70, col 2, para 2), ii) a Jun Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2, and iii) wherein PIII is the phage coat protein comprising the pelB signal sequence (i.e.: a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic

membrane in an essentially unfolded state; see p 70, col 1, para 4, col 2, para 2, Fig. 1), and b) a second fusion protein comprising: i) a cDNA from a cDNA library (i.e.: protein or protein fragment), ii) a Fos Leucine zipper interaction domain (see p 70, col 1, para 4, col 2, para 2), and iii) a pelB signal sequence (i.e.: a protein translocation sequence which effects that the fusion protein upon expression in a bacterium is translocated through the cytoplasmic membrane), wherein the interaction domain of the first fusion protein can bind to those of the second fusion protein (throughout document, see particularly p 70, col 1, para 4, Fig. 1).

Regarding present **claim 3**, Crameri et al. teach a second fusion protein comprising a cDNA from a cDNA library (see p 70, col 1, para 4, Fig. 1).

Regarding **claims 4-5**, Crameri et al. teach the M13 pIII phage coat protein (see p 70, col 2, para 2).

Regarding **claim 6**, Crameri et al. teach the first fusion protein with a Jun leucine zipper interaction domain and the second fusion protein with a Fos leucine zipper interaction domain (see p 70, col 2, para 2).

Regarding **claim 7**, Crameri et al. teach wherein the first fusion protein comprises the pelB signal sequence (i.e.: Sec-dependent signal sequence; see p 70, col 1, para 4, col 2, para 2, Fig. 1).

Regarding **claim 9**, Crameri et al. teach covalent linking of the Jun and Fos leucine zippers (i.e.: the first fusion protein is covalently bound to the second fusion protein through the leucine zippers; see p 70, col 1, para 4, Fig. 1).

Although Crameri et al. teach first and second fusion proteins covalently bound, Crameri et al. do not teach a second fusion protein comprising a Tat-dependent translocation sequence.

Regarding present **claims 1 and 8**, Georgiou et al. teach a Tat-dependent translocation sequence that transports the folded proteins it is fused to through the cytoplasmic membrane (Throughout document, see particularly columns 1,2 and examples 7 and 8).

It would have been obvious to one of skill in the art to use the Tat-dependent translocation sequence taught by Georgiou et al. in the fusion protein mixture taught by Crameri et al. One would have been motivated to do so to take advantage of the ability of the Tat pathway to transport folded proteins. One would have had a reasonable expectation for success because Georgiou et al. teach that the Tat-dependent translocation sequences translocate functional folded proteins through the cell membrane (throughout document, see particularly examples 7 and 8). Therefore, the teachings of Crameri et al. and Georgiou et al. render the present invention to be *prima facie* obvious.

Response to Arguments

Applicant's arguments filed December 16, 2009 have been fully considered but they are not persuasive for the following reasons.

In response to applicants arguments that Crameri et al. do not teach the limitation of the second fusion protein comprising a translocation sequence that leads to translocation in a folded state, it is noted that the limitations regarding folding state (e.g.: that the fusion protein is translocated in an essentially folded or unfolded state) are not given patentable weight because they are interpreted as a process of making and not the end product currently claimed (e.g.: a specific structure that would provide different folding requirements is not presently in the claims). Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does

not depend on its method of production. If the product in the product by process claim is the same as or obvious from a product of the prior art, the claim is unpatentably distinct even though the prior product was made by a different process, *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966(Fed. Cir. 1985).

The structure implied by the process steps should be considered when assessing the patentability of product -by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would by expected to impart distinctive structural characteristics to the final product, See e.g., *In re Garnero*, 412 F. 2d 276, 279, 162 USPQ 221, 223 (CCPA 1979). Applicants do not currently have a specific structure (e.g.: a specific sequence) in the claims that would provide specific folding requirements.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, all the references teach proteins with translocation sequences relating to folding and transportation into the periplasmic space or extracellular matrix. In addition, Georgiou et al. state:

"Proteins exported through the TAT system first fold into their native conformation within the cytoplasm and are then exported across the cytoplasmic membrane. The ability to export proteins that have already folded in the cytoplasm is highly desirable with regard to commercial protein production for several reasons. First of all, proteins that fold very rapidly

after synthesis is completed cannot be secreted by the more common sec export pathway. Secondly, the bacterial cytoplasm contains a full complement of folding accessory factors, which can assist a nascent polypeptide in reaching its native conformation. In contrast, the secretory compartment of bacteria contains very few folding accessory factors such as chaperones and foldases. Therefore, for the production of many proteins, it is preferable for folding to occur first within the cytoplasm followed by export into the periplasmic space through the TAT system. Thirdly, the acquisition of cofactors has to occur within the cytoplasm concomitant with folding. Consequently, cofactor-containing proteins must be secreted through the TAT pathway." (See col 5).

Therefore, one of skill in the art would have been motivated to utilize the Tat sequence taught by Georgiou et al. inorder to take advantage of the benefits taught by Georgiou et al.

Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute one known element (i.e.: the Tat translocation sequence taught by Georgiou et al.) for another known element (i.e.: the PelB translocation sequence taught by Crameri et al.) because it would have yielded the predictable result of a folded protein. See *KSR International Co. v. Teleflex Inc.*, USPQ2d 1385 (U.S. 2007).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that one of the fusion proteins is folded in the cytoplasm and is subsequently transported into the periplasm, where it can bind to another fusion protein which has been folded in the periplasm) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, the limitation that the first fusion protein and second fusion protein are covalently or non-covalently bound is not required to take place in any particular location (e.g.: it is not required to take place in a cell) and therefore applicants arguments regarding whether a protein folded in the cytoplasm would interact with a protein folded in the periplasm do not apply.

In response to applicants arguments that Crameri et al. teach away from the claimed invention, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). See MPEP § 2123. In addition, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). See MPEP § 2141.06 IV. The fact that Crameri et al. do not contemplate the use of a Tat translocation sequence does not constitute "teaching away". In addition, the fact that Crameri et al. state "the potential for the expression of dimmers is mainly limited by the imagination of the investigator" would indicate that Crameri et al. are encouraging investigators to be creative and contemplate other possibilities.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Future Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHANNON JANSSEN whose telephone number is (571)270-1303. The examiner can normally be reached on Monday-Friday 9:00AM-6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amber D. Steele/
Primary Examiner, Art Unit 1639

Shannon L Janssen